NJC

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

rsc.li/njc

View Article Online
DOI: 10.1039/C8NJ02037J

Journal Name

ARTICLE

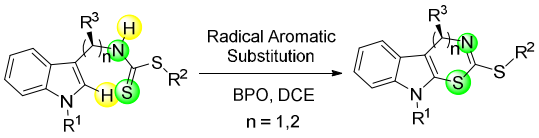
A concise synthesis of cyclobrassinin and its analogues via thiyl radical aromatic substitution

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Xin Zhong, Ning Chen*, Jiaxi Xu*



Abstract: A simple and concise approach for the synthesis of cyclobrassinin has been developed through a thiyl radical-mediated intramolecular aromatic substitution, with benzoyl peroxide as efficient initiator and oxidant. The current method can also be utilized in the synthesis of 6 and 7-membered ring cyclobrassinin analogues in moderate to good yields. The transformation undergoes a formal radical 6 and 7-*endo*-trig cyclization of the corresponding dithiocarbamate derivatives, which were generated from indole-3-methanamines and tryptophan.

Introduction

As typical molecules of cruciferous phytoalexins, cyclobrassinin and its analogues play notable roles in the plant disease resistance,[1-3] human health,[4] and soil ecology.[5,6] Moreover, high consumption of cruciferous vegetables is also known as lowering the risk of human diseases like lung and colorectal cancers.[4] General methods to obtain such indole-sulfur-containing phytoalexins are designed through biosynthesis, but with low efficiency in transformations.[7-9] More effective approaches are designed by chemical synthesis, most of which have been developed through the oxidation of brassinin by use of bromination oxidants, such as NBS (*N*-bromosuccimide),[1] pyridinium tribromide,[10] dioxane dibromide,[11] and $PhMe_3NBr_3$.[12] In such transformations, sulfenyl bromide intermediates are *in situ* generated. The electrophilic sulfenyl bromides undergo an intramolecular aromatic substitution with the indole moiety to afford cyclobrassinin [Scheme 1, *eqn* (1)]. To our best knowledge, there is still no approach that utilizes the thiyl radical aromatic substitution to realize the synthesis of cyclobrassinin and its analogues through the aromatic carbon-sulfur bond formation. Although thiyl radicals have been identified as weak electrophilic radicals,[13] they preferably react with olefins rather than arenes probably due to the high activation energy in the dearomatization step during reaction process.

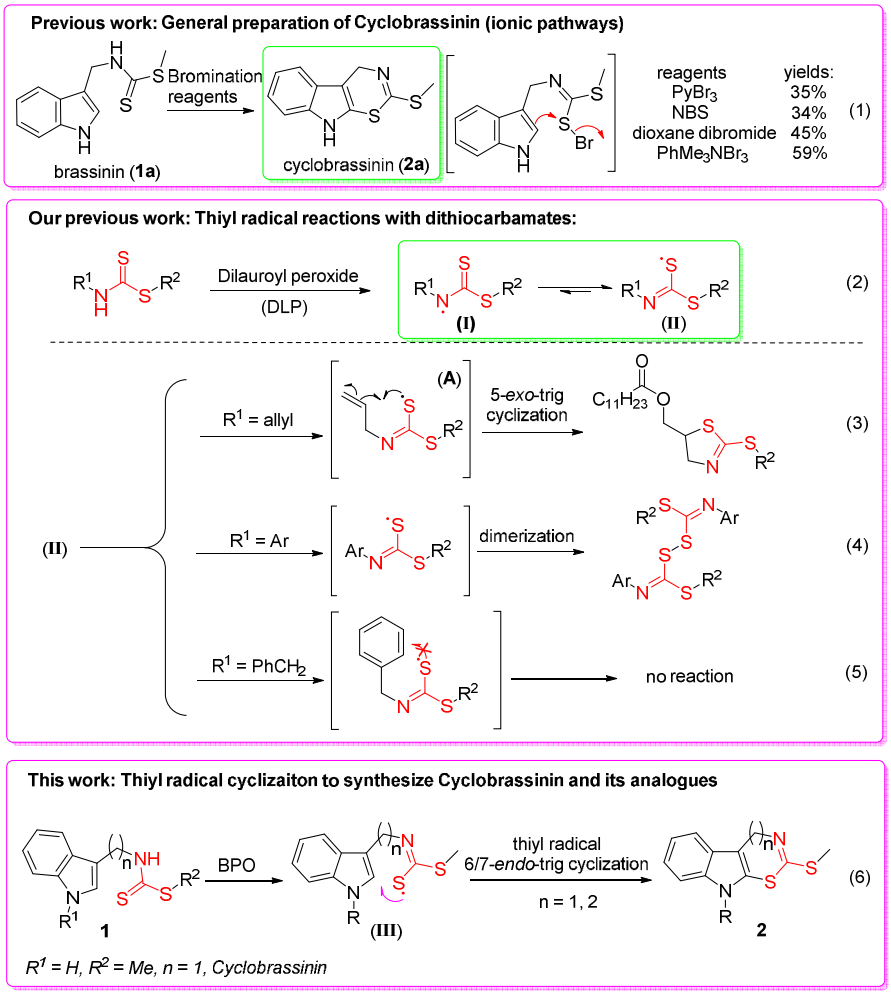
To develop a new chemical transformation is always exciting and challenging. The formation of the aromatic C-S bond has been usually realized from the transition-metal-catalyzed cross-coupling of aryl halides (or sulfonates) with thiols or disulfides.[9,14,15] The recent methodologies fascinate the direct oxidative dehydrogenative C-H/S-H cross-coupling of arenes and thiophenols, some of which proceed under the thiyl radical mechanism.[16-20] Generally, thiyl radicals play a significant role in the construction of carbon–carbon and carbon–heteroatom bonds and display broad applications in organic synthesis,[21-23] pharmaceutical synthesis,[24] and polymer preparations.[25-27] In these cases, all thiyl radicals are generated from thiols or disulfides, none of which is obtained from dithiocarbamates. Recently, our group disclosed that *N*-substituted dithiocarbamates were used as active thiyl radical (**II**) precursors (Scheme 1, *eqn (2)*).[28,29] Interestingly, when *N*-substituents are allyl groups,[28] the active thiyl radicals are captured by the electron-rich olefins in the allyl group to afford thiazoline derivatives (*eqn (3)*).[13] However, when *N*-substituents are aryl groups,[29] the *in situ* generated thiyl radicals prefer dimerization to the aromatic radical substitution probably due to their low electrophilicity caused by the delocalization effect of the aryl groups (*eqn (4)*). To circumvent the conjugation effect of aryls with thiyl radicals, *N*-benzyl dithiocarbamates were investigated, but no target molecule was obtained possibly because of difficult dearomatization of a phenyl ring (*eqn (5)*). As we known, the aromaticity of pyrrole is weaker than that of benzene, thus comparing with benzene, the dearomatization of pyrrole should be easier. Moreover, to fascinate the radical aromatic substitution , a more electron-rich arene, like indole, might be more reactive. Therefore, we rationalized that alkyl

[a] State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China.
Email: chenning@mail.buct.edu; jxxu@mail.buct.edu.cn.

Electronic Supplementary Information (ESI) available: [Copies of ^1H and ^{13}C NMR spectra of dithiocarbamates **1** and cyclobrassinin **2** and its analogues]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C8NJ02037J

N-(indol-3-yl)alkyldithiocarbamates should be suitable substrates for the synthesis of cyclobrassinin and its analoguesthrough radical aromatic electrophilic substitution. We, herein, report the synthesis of cyclobrassinin and its analogues from *N*-(indol-3-yl)alkyldithiocarbamates through a formal 6/7-*endo*-trig radical cyclization (intramolecular radical aromatic substitution).



Scheme 1. Synthesis of Cyclobrassinin and dithiocarbamate radical chemistry.

Results and discussion

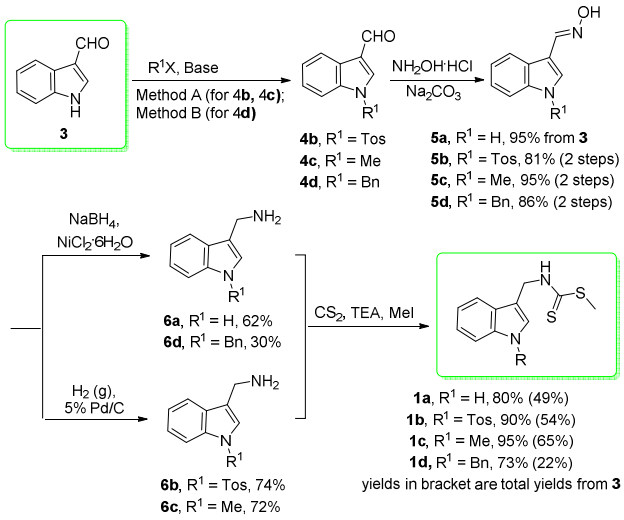
Synthesis of Brassinin (1a) and its dithiocarbamate analogues (1b–1h)

To begin our study, all methyl *N*-(indol-3-yl)alkyldithiocarbamates **1** were synthesized from the corresponding (indol-3-yl)alkylamines (or their hydrochloride salts), carbon disulfide, and alkyl halides,[28] or from (indol-3-yl)alkyl isothiocyanoates and mercaptans.[29] The corresponding amines (or their hydrochloride salts) were prepared according to the literature procedure or a modified procedure of literature.[30-32]

Brassinin (**1a**), the model reaction substrate, and its analogues, were synthesized from indole-3-carbaldehyde (**3**) in 3 to 4 steps (Scheme 2). Initially, brassinin (**1a**) was obtained from indole-3-carbaldehyde (**3**) through a reductive amination with hydroxyamine hydrochloride followed by a direct condensation with carbon disulfide and methyl iodide in a total yield of 49% for three steps. In the synthesis of *N*-substituted brassinins **1b-d**, (*N*-substituted indol-3-yl)methanamines **6** were prepared from **3** through a substitution followed by a reductive amination via their oxime intermediates. Two approaches were examined for the reduction of oximes **5** to amines **6.** *N*-Benzyl indole-3-carbaldehyde oxime (**5d**) was reduced with $NaBH_4$ under the aid of the $NiCl_2$ promotion. *N*-Tosyl and *N*-methyl indoles **5b** and **5c** were reduced under the catalytic hydrogenation in the presence of Pd/C. Treatment of **6** with carbon

View Article Online
DOI: 10.1039/C8NJ02037J

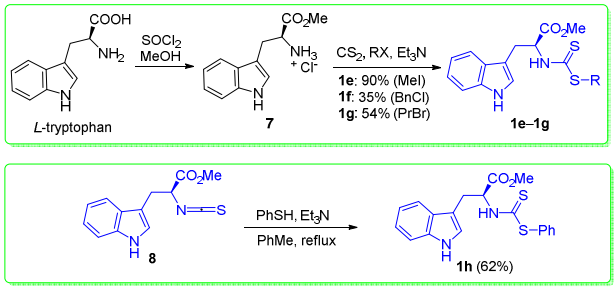
disulfide and methyl iodide directly resulted in the formation of brassinin (**1a**) and its analogues **1b**–**1d** in good to excellent yields.



Reagents and conditions: Method A: TsCl (for **4b**) or MeI (for **4c**), TBAB (0.1 equiv), NaOH (50% aq)/C_6H_6 = 1:1, 4 h; Method B: BnBr (1.1 equiv), Cs_2CO_3 (1.1 equiv), reflux for 2 h in dry CH_3CN.

Scheme 2. Synthesis of brassinin (**1a**) and its analogues (**1b**–**1d**).

For further application, we envisioned that tryptophan, a naturally occurring indole alkylamine derivative, might also be an effective substrate in this reaction. More significantly, tryptophan is also the raw material for biosynthesis of brassinin under enzyme catalysis.[8] Thus, tryptophan-based dithiocarbamates **1e–1g** with various *S*-substituents were designed as following (Scheme 3). First, methyl *L*-tryptophanate hydrochloride (**7**) was synthesized from *L*-tryptophan in a quantitative yield according to literature.[32] The following treatment with carbon disulfide and alkyl halides in the presence of Et_3N gave rise to substrates **1e**–**1g** in moderate to good yields. In the preparation of **1f** from **7** and benzyl chloride, thioisocyanate **8** was generated as a byproduct with 22% yield of isolated product under the column chromatography. We thus reacted **8** with thiophenol to prepare *S*-phenyl substituted substrate **1h** in 62% yield.



Scheme 3. Synthesis of dithiocarbamates **1e**–**1h** from *L*-tryptophan.

Synthesis of Cyclobrassinin and its analogues via thiyl radical aromatic substitution

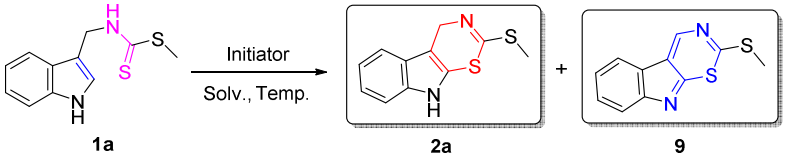
The thiyl radical cyclization was commenced with brassinin (**1a**) as a model substrate (Table 1). Generally, dilauroyl peroxide (DLP) has been used as the efficient initiator to trigger the radical initiation of xanthates and dithiocarbamates,[33,34] but in the current case, its initiation only produced cyclobrassinin (**2a**) in a very poor yield, while most of brassinin (**1a**) was recovered (Table 1, entries 1 & 2). The yield was slightly increased when additional 1 equiv. of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was added, but an over-oxidation product, dehydrocyclobrassinin (**9**), was also detected in 6% yield (Table 1, entry 3). Although it is a widely-used dehydrogenation reagent, DDQ showed no reactivity in the reaction when it was used as the sole dehydrogenation reagent (Table 1, entry 4). To our best knowledge, benzoyl peroxide (BPO) was seldom used as the initiator in xanthate chemistry because of its poor efficiency,[33-35] but, herein, the reaction efficiency was obviously promoted when it was applied (Table 1, entry 5). Moreover, increasing amount of BPO from 1.0 to 1.5 equiv. improved the product yield to 42% (Table 1, entry 6). Such intramolecular oxidative coupling that the homolytic aromatic substitution requires over 1.0 equiv. initiator has been previously discovered in the system of ArX/Bu_3SnH (2.2 equiv.)-AMBN (1.0 equiv.),[36] ArI/Bu_3SnH (2.0 equiv.)-AIBN (1.0 equiv.),[37] and ArBr/Bu_3SnH (3.7 equiv.)-AIBN (1.0 equiv.).[38] In these transformations, equimolecular AIBN or AMBN, obviously acted as not only an initiator to trigger the $Bu_3Sn^{\cdot}$ Radical, but also an oxidant to convert the 5-electron π-radical intermediates into the cyclized arenes or heteroarenes in the rearomatization steps. Similar results were also demonstrated by Zard in their stoichiometric DLP-triggered homolytic aromatic substitution from the arylalkyl xanthate intermediates.[33,39] The screening of solvents indicated that only 1,2-dichloroethane (DCE) and toluene (PhMe) provided moderate yields, but DCE had better selectivity (Table 1, entries 6–8). Experimental results from entries 9–11 demonstrated alkyl peroxides, such as di-*t*-butyl peroxide (DTBPO), *tert*-butyl peroxide (TBPO), and *tert*-butyl peroxybenzoate (TBPBO), provided no desired products at neither 80 °C in DCE nor at 132 °C in chlorobenzene. The addition of metal catalyst diminished the product yield (Table 1, entry 12). Finally, microwave irradiation was tested (30 min), but it was still hard to promote the reaction efficiency (Table 1, entry 13).

View Article Online
DOI: 10.1039/C8NJ02037J

Journal Name

ARTICLE

Table 1. Optimization of the intramolecular thiyl radical cyclization



Entry	Initiator (equiv.)	Solvent	Temp (°C)	Yield[a] (%)	
				2a	**9**
1	DLP (1.0)	DCE	83	<1	trace
2[b]	DLP (1.5)	DCE	83	5	trace
3	DLP (1.5), DDQ (1.0)	DCE	83	8	6
4	DDQ (1.0–2.0)	CH_3CN	r.t. to 80	N.D.	1
5	BPO (1.0)	DCE	83	17	1
6	BPO (1.5)	DCE	83	42	7
7	BPO (1.5)	PhMe	110	43	12
8	BPO (1.5)	CH_3CN	81	36	17
9[c]	DTBPO (1.0)	DCE/PhCl	80/132	trace	N.D.
10	TBPO (1.0)	DCE/PhCl	80/132	trace	N.D.
11	TBPBO	DCE/PhCl	80/132	Trace	N.D.
12	BPO (1.5), $Cu(OTf)_2$ (0.2)	DCE	83	3	18
13	BPO (1.5), MW[d] (0.5 h)	DCE	83	34	9

a) Yields of isolated products are given. b) Reaction time was prolonged to 4 h. c) N. D. not detected. 80 °C for DCE, 132 °C for PhCl. d) MW = Microwave irradiation.

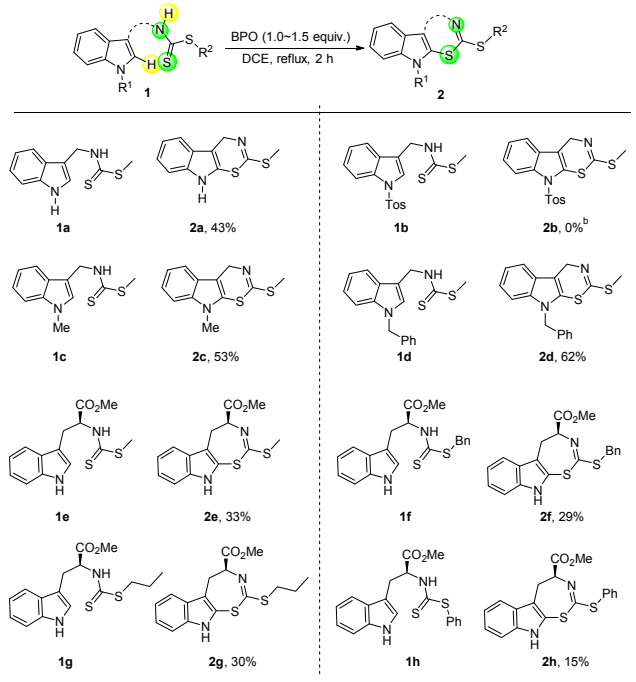
With the optimized conditions in hand, we further investigated the reaction scope and the effect of *N*-substituents on the indole ring and *S*-substituents on dithiocarbamates. Notably, although 1.5 equiv. of BPO were required for *N*-H and *N*-tosyl substrates (**1a** and **1b**), only 1.0 equiv. of BPO was enough for *N*-alkyl substrates **1c** and **1d** to consume all starting materials according to the monitor of TLC and ^{1}H-NMR analyses. The reaction results are summarized in Table 2. Obviously, the electron-withdrawing tosyl group on the nitrogen atom of indole is unfavourable to the reaction. Substrate **1b** gave rise to a complex system under optimized conditions and no target compound **2b** was detected through the analyses of both NMR and HRMS analyses. Curran identified that 2-halo-*N*-((1-tosylindolin-3-yl)methyl)anilines could be converted to the corresponding spiroindoline products by Bu_3SnH/AIBN involving a *5-exo*-trig cyclization followed by a *β-fragmentation* of tosyl group to afford cyclic imines.[40,41] In our case, only a trace yield of spirocyclic imine **G** (scheme 4) was generated in the reaction system determined by ^{1}H NMR and HR-MS. Instead, the corresponding isothiocyanate **8** was isolated as a major side product in 17% yield (the detailed

View Article Online
DOI: 10.1039/C8NJ02037J

information are listed in Supporting Information, see pages S3 and S4).

Dithiocarbamates **1c** and **1d** with electron-donating alkyl groups (Me and Bn) promoted the yields to 53% and 62%, respectively. The results indicate that electron-rich indoles show more efficient than the electron deficient ones because α-imino thiyl radicals are electrophilic.[8] In summary, electron-donating alkyl groups (Me and Bn) on the nitrogen atom not only greatly enhanced the electron density of the indole ring, but also effectively inhibited the further oxidation to afford the undesired dehydrocyclobrassinin (**3a**).

Table 2. *N*-Substituent effect on the 6-*endo*-trig thiyl radical cyclization[a]



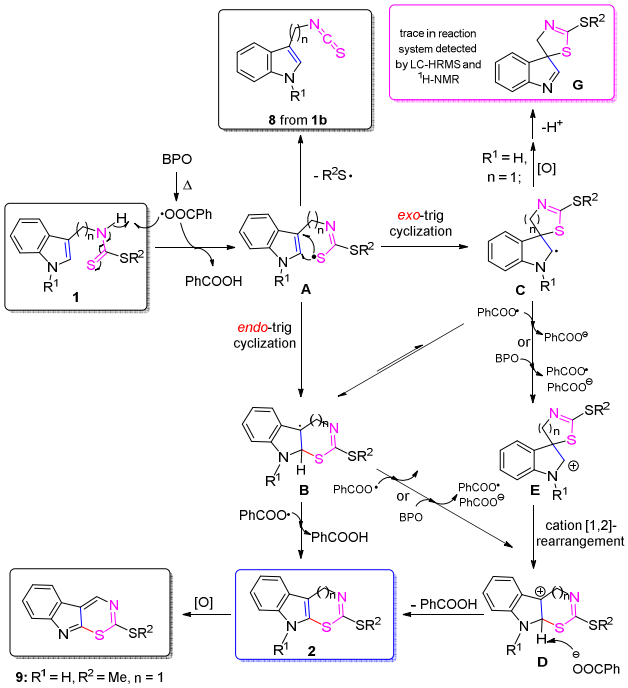
[a] Reactions were conducted on a 0.3 mmol scale of **1** in 2.5 mL of dry DCE. [b] The reaction system was very complicated and the corresponding isothiocyanate **8** was isolated as a major product in 17% yield.

After synthesis of cyclobrassinin (**2a**) and its analogs (**2c** and **2d**), we next turned to investigate the synthesis of seven-membered cyclobrassinin analogs from tryptophan-derived dicarbamates and the influence of *S*-substituents of dithiocarbamates with substrates **1e**–**1g**. As shown in Table 2, all *S*-alkyl substrates, such as methyl (**1e**), benzyl (**1f**), and *n*-propyl (**1g**), afforded the corresponding intramolecular cyclization products with the similar isolated yields range from 29% to 33%. In these transformations, no oxidized products, analogues of **9**, were detected. In comparison, *S*-phenyl substrate **1h**, bearing an aromatic substituent, only produced the desired product **2h** in 15% yield. Increasing the loading of BPO to 1.5 and 2 equivalents did not improve the reaction efficiency. The reaction system was also much more complicated than those of **1e**, **1f**, and **1g**, and the cyclization product **2h** was always mixed with a little amount of an unknown byproduct with the similar polarity (almost same R_f value with different eluents), which was hard to be removed by column chromatography. The results demonstrate that both *S*-alkyl and *S*-aryl substituted dithiocarbamates afford the cyclization products in moderate yields because the formation of the seven-membered ring is more difficult than the generation of the six-membered ring in the radical aromatic substitution.

Proposed mechanism for the radical cyclization process

Finally, on the basis of our previous work,[28,29,35] and insights on the thiyl radical reactions of dithiocarbamates, a plausible mechanism was proposed in Scheme 4. Generally, BPO acts as both the radical initiator and the oxidant. First, BPO dissociates under heating to produce a benzoyloxy radical, which then abstracts a hydrogen atom from dithiocarbamates **1** to yield the electrophilic α-imino thiyl radicals **A**. Active radials **A** can attack both 2- and 3-positions of the indole ring *via* an *endo*-trig or *exo*-trig type cyclization to generate tertiary benzyl radicals **B** or secondary carbon radicals **C**, respectively. Generally, radicals **B** are more thermodynamically stable, but radicals **C** are more kinetically favoured because *5-exo*-trig cyclization is much more efficient than *6-endo*-trig according to the Baldwin rule.[42,43] In the *6-endo*-trig pathway, intermediates **B** could directly lose a hydrogen through abstraction by the benzoyloxy radical to afford the target cyclobrassinin **2**, or are first oxidized by the benzoyloxy radical to generate cations **D**, which lose a proton to afford **2**. Both pathways are possible, especially the latter one when the radicals are stabilized by an adjacent electron-donating substituent.[34] While in the *5-exo*-trig pathway, spiro-intermediates **C** are generated. Subsequently, intermediates **D** are generated through an oxidation of **C** by the benzoyloxy radical followed by a cation rearrangement. To identify the possibility, we analyzed the reaction system with LC-HRMS and ^{1}H-NMR. Both spectroscopic analyses showed the trace existence of spiro-intermediates **G** (see supporting information, pages S5 and S6). Moreover, if indole is electron-deficient **1b**, the electrophilic thiyl radical **A-1b** could not attack the indole, so it prefers to lose an alkylthio radical to provide the corresponding isothiocyanate **8**.

View Article Online
DOI: 10.1039/C8NJ02037J



Scheme 4. A plausible mechanism of thiyl radical cyclization of **1**.

Conclusions

In summary, we have developed a simple approach for the synthesis of cyclobrassinin and its 6- and 7-membered-ring analogues. Inole-3-carbaldehyde was used as starting materials to provide brassinin and its analogues through the reductive amination with hydroxyamine hydrochloride followed by a direct condensation with carbon disulfide and methyl iodide in three to four steps. After esterification with methanol, *L*-tryptophan was converted into its carbamates in moderate to good yields through the reaction with carbon disulfide and various alkyl halides. During the following cyclization, benzoyl peroxide was found as the efficient initiator to promote the intramolecular radical aromatic electrophilic substitution *via* a formal 6 and 7-*endo*-trig cyclization process. The formation mechanism of cyclobrassinin was proposed through both 5-*exo*-trig and 6-*endo*-trig cyclization. Finally, the current process can be utilized in the synthesis of cyclobrassinin and its 6 and 7-membered-ring analogues.

Experimental

Unless otherwise noted, all materials were purchased from commercial suppliers. Flash column chromatography was performed using silica gel (normal phase, 200-300 mesh) from Branch of Qingdao Haiyang Chemical Industry. Petroleum ether (PE) used for column chromatography is 60–90 °C fraction, and the removal of residue solvent was accomplished under rotovap. Reactions were monitored by thin-layer chromatography on silica gel GF254 coated 0.2 mm plates from Institute of Yantai Chemical Industry. The plates were visualized under UV light. All commercially available reactants were used directly. 1,2-Dichloroethane (DCE) is dehydrated with CaH_2 under refluxing. Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were measured with a Bruker 400 spectrometer in $CDCl_3$ and DMSO-d_6 with tetramethylsilane (TMS). IR spectra were recorded directly on a Nicolet AVATAR 330 FTIR spectrometer. HRMS spectra were determined with an Agilent Liquid Chromatography/Mass Spectrometry/Data and Time-of-Flight (LC/MSD TOF) mass spectrometer.

Synthesis of Brassinin (1a) and its dithiocarbamate analogues (1)

Synthesis of 1a and 1d

Procedure for the synthesis of 4d

Indole-3-carboxaldehyde (2.9 g, 20 mmol) and Cs_2CO_3 (13 g, 40 mmol) were dissolved in 150 mL of dry acetonitrile and the reaction mixture was refluxed for 2.5 h. Then BnBr (3.76 g, 2.6 mL, 22 mmol) was added into the reaction system which was then refluxed for 1 h. After evaporation of solvent in vacuum, water was added (150 mL) and the aqueous phase was extracted with EtOAc (3 × 150 mL), the organic layer was dried over anhydrous Na_2SO_4. The crude product was obtained in a quantitative yield after evaporation of EtOAc and was used for the next step without further purification.

Procedure for the synthesis of 5a and 5d

To a solution of indole-3-carboxaldehyde (**3**, 1.96 g, 13.5 mmol) or 1-benzyl-indole-3-carboxaldehyde (**4d**, 3.18 g, 13.5 mmol) in a mixture of ethanol (90 mL) and water (9 mL) were added hydroxyamine hydrochloride (1.61 g, 23.1 mmol) and anhydrous sodium carbonate (1.11 g, 10.5 mmol). The mixture was stirred for 30 min at room temperature (for **3**) or 1 h at 60 °C (for **4d**). After evaporation of solvent in vacuum, water (90 mL) was added and the aqueous phase was extracted with EtOAc (3 X 120 mL). The organic phase was collected and then dried over anhydrous Na_2SO_4. After removal of EtOAc, the crude oxime **5a** (2.1 g) or **5d** (2.9 g) was obtained with the yield of 98% and 86%, respectively.

Procedure for the synthesis of 6a and 6d

To a solution of the crude oxime **5a** (1.0 g, 6.2 mmol) or **5d** (1.6 g, 6.4 mmol) in methanol (120 mL) was added nickel(II) chloride hexahydrate puratrem (1.63 g, 6.86 mmol). The system was cooled to 0 °C by an ice water bath, and then sodium borohydride (1.65 g, 43.7 mmol) was added in one portion. A black precipitate was generated in 5 min and was filtered off. The filtrate was concentrated in vacuum to approx. 30 mL and was poured into 200 mL of ammonia water (0.67 mol/L: 10 mL ammonia water (25%) in 190 mL of deionized water). After extraction with EtOAc (3 × 200 mL), the organic layer was dried over anhydrous Na_2SO_4 followed by an evaporation of the solvent, the crude amine **6a** (0.78 g) or **6d** (1.21 g) was obtained as a viscous and yellowish oil. Pure **6a** was obtained as colorless crystals after column chromatograph with $CHCl_3$/MeOH/TEA = 80:20:1 as eluent. 565 mg, yield 62%, mp. 124 – 127 °C ($CHCl_3$/MeOH), lit. mp. 102 – 104 °C (DCM/*n*-Hexane).[30] ^{1}H

View Article Online
DOI: 10.1039/C8NJ02037J

NMR (400 MHz, DMSO-d_6): δ = 11.15 (s, 1H, NH), 7.66 (d, *J* = 7.6 Hz, 1H, ArH), 7.37 (m, 2H, ArH), 7.10 (dt, *J* = 0.8, 7.6 Hz, 1H, ArH), 7.01 (dt, *J* = 0.8, 7.6 Hz, 1H, ArH), 5.21 (br. s, 2H, NH_2), 4.01 (s, 2H, CH_2) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 136.2, 126.3, 124.1, 121.2, 118.6, 118.5, 112.4, 111.5, 35.4 ppm. The crude **6d** was used directly in the next step reaction without further purification.

Procedure for the synthesis of 1a and 1d

To a solution of **6a** (565 mg, 3.86 mmol) or crude **6d** (1.21 g) in 20 mL of methanol was added TEA (1.17 g, 1.61 mL, 11.6 mmol), CS_2 (882 mg, 0.70 mL, 11.6 mmol), and MeI (1.64 g, 0.72 mL, 11.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and warmed up to room temperature for 2 h. After evaporation of solvent in vacuum, water (40 mL) was added followed by an extraction of EtOAc (3 × 30 mL and 2 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was then removed in vacuum. The pure dithiocarbamates **1a** (729 mg) and **1d** (210 mg) were obtained after the purification of column chromatography with PE/EtOAc = 20/1–10/1–7/1 as eluent.

Methyl ((*1H*-indol-3-yl)methyl)carbamodithioate (Brassinin, 1a)

Pale yellow solid, the three-step yield was 49% with indole-3-carboxaldehyde (**3**) as starting material. M.p. 135–137 °C ($CHCl_3$/MeOH) lit. m. p. 133 – 135 °C (DCM/ *n*-Hexane).[12] IR ($CHCl_3$) (cm^{-1}): 3406, 3324, 2918, 1498, 1080, 918, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H, NH), 7.62 (d, *J* = 8.0 Hz, 1H, ArH), 7.39 (d, *J* = 8.0 Hz, 1H, ArH), 7.23 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H, 6-H overlapped with 2-H), 7.16 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H, ArH), 7.03 (br s, 1H, NH), 5.04 (d, *J* = 3.6 Hz, 2H, CH_2), 2.63 (s, 3H, SCH_3) and minor signals (1/4 intensity of the major ones) due to a rotamer at δ = 7.85 (br. s, NH), 4.76 (d, *J* = 4.0 Hz, 2H, CH_2), 2.73 (s, SCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.2, 136.2, 126.4, 124.0, 122.8, 120.3, 118.7, 112.4, 111.4, 43.2, 18.1.

***N*-(1-Benzyl-*1H*-indol-3-yl)methyl-*S*-methyl dithiocarbamate (1d)**

White solid, 210 mg, the four-step yield was 22% with indole-3-carboxaldehyde (**3**) as starting material, m.p. 146–148 °C (PE/EA). IR ($CHCl_3$) (cm^{-1}): 3335, 2917, 1495, 1467, 1301, 1076, 920, 742. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.6 Hz, 1H, ArH), 7.32 – 7.13 (m, 9H, ArH), 7.00 (br s, 1H, NH), 5.29 (s, 2H, CH_2Ar), 5.04 (with a minor rotamer signal at 4.77)(d, *J* = 4.0 Hz, 2H, CH_2N), 2.64 (with a minor rotamer signal at 2.74)(s, 3H, SCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.0, 136.9, 136.7, 128.9, 127.9, 127.8, 127.2, 126.9, 122.5, 120.0, 118.9, 110.1, 109.8, 50.1, 43.2, 18.1. HRMS (ESI), *m/z*, calcd for $[M+Na]^+$: $C_{16}H_{18}N_2NaS_2^+$, 349.0804. Found: 349.0798.

One-pot procedure for the synthesis of 1b and 1c

To a solution of indole-3-carboxaldehyde (**3**, 2.0 g, 13.8 mmol) in benzene (50 mL) were added an aqueous sodium hydroxide solution (50 mL, 30% *wt.*), tetrabutylammonium bromide (440 mg, 1.38 mmol), and TsCl (2.76 g, 14.4 mmol, for **4b**) or MeI (1.96 g, 0.86 mL, 13.8 mmol, for **4c**). The mixture was stirred at room temperature and monitored with TLC. When the reaction was finished, the benzene layer was separated and water layer was extracted with benzene (2 × 20 mL). After drying over anhydrous Na_2SO_4 and evaporation of benzene, the corresponding crude aldehyde **4b** or **4c** was obtained in 100% and 95% crude yields, respectively. They were used directly in the next step reaction without further purification.

To a solution of the crude **4b** (4.04 g) or **4c** (2.15 g) in ethanol (90 mL) and water (9 mL) were added hydroxylamine hydrochloride (1.61 g, 23.1 mmol) and anhydrous sodium carbonate (1.11 g, 10.5 mmol). The mixture was stirred for 30 min at 90 °C (for **4b**) or at room temperature for 3 h (for **4c**). After evaporation of ethanol, water (90 mL) was added and followed by an extraction with EtOAc (3 × 120 mL). After drying over anhydrous Na_2SO_4, the organic phase was removed in vacuum and the crude oximes **5b** (3.4 g) and **5c** (2.9 g) were obtained with the yields of 81% and 100%, respectively.

5% Pd on C (300 mg) and 36%wt HCl (4 mL) were added into a solution of the crude oxime **5b** (2.2 g) or **5c** (1.3 g) in methanol (60 mL). The suspension was stirred under H_2 (10 bar) at room temperature overnight. After filtration on celite, the solvent was evaporated. The residue was dissolved in EtOAc (25 mL) and water (30 mL), then 2 mol/L NaOH aqueous solution was added to the solution to adjust the pH to 11. The water layer was extracted with EtOAc (3 × 40 mL) and organic layer was dried over Na_2SO_4. After removal of solvent, the crude amines **6b** and **6c** were obtained and used directly in the following step. The *in situ* generated **6b** or **6c** was dissolved in a mixture of methanol (30 mL) and EtOAc (20 mL) and the system was cooled to 0 °C in an ice water bath. TEA (1.82 g, 2.5 mL, 18.0 mmol), CS_2 (1.37 g, 1.1 mL, 18.0 mmol), and MeI (2.55 g, 1.1 mL, 18.0 mmol) were added into the reaction system in sequence. The mixture was stirred at 0 °C for 10 min and then warmed up to room temperature for 2 h. After removal of solvent, water (60 mL) was added and followed by extraction with EtOAc (3 × 70 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed. Pure dithiocarbamates **1b** (1.83 g) and **1c** (1.20 g) were obtained after the purification of column chromatograph with PE/EA = 20/1 – 10/1 – 7/1 as eluent.

S-Methyl-*N*-(1-(p-toluenesulfonyl)-*1H*-indol-3-yl)methyl dithiocarbamate (1b)

Yellow solid, 1.83 g, the four-step yield was 54% with indole-3-carboxaldehyde (**3**) as starting material, m.p. 114–116 °C ($CHCl_3$). IR ($CHCl_3$) (cm^{-1}): 3326, 2920, 1596, 1494, 1369, 1172, 979, 746. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 7.77 (d, *J* = 8.4 Hz, 2H, ArH), 7.57 (s, 1H, ArH), 7.53(d, *J* = 8.0 Hz, 1H, ArH), 7.35 (dd, *J* = 7.6, 8.0 Hz, 1H, ArH), 7.27 – 7.22 (m, 3H, ArH), 7.04 (br. s, NH), 5.02 (d, *J* = 4.4 Hz, 2H, CH_2N), 2.65 (s, 3H, SCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 199.3, 145.2, 135.2, 135.0, 130.0, 126.9, 126.7, 125.3, 125.1, 123.6, 119.6, 117.3, 113.7, 42.4, 21.6, 18.3. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{18}H_{19}N_2O_2S_3^+$, 391.0603. Found: 391.0603.

***N*-(1-Methyl-1H-indol-3-yl)methyl-*S*-methyl dithiocarbamate (1c)**

Yellow solid, 1.20 g, the four-step yield was 65% with indole-3-carboxaldehyde (**3**) as starting material, m.p. 114–116 °C ($CHCl_3$). IR

View Article Online
DOI: 10.1039/C8NJ02037J

($CHCl_3$) (cm^{-1}): 3321, 2916, 1475, 1388, 1301, 1074, 919, 742. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (d, *J* = 8.0 Hz, 1H, ArH), 7.27 (dd, *J* = 7.2, 8.0 Hz, 1H, ArH), 7.15(dd, *J* = 7.2, 8.0 Hz, 1H, ArH), 7.09(s, 1H, ArH), 7.02 (br. s, NH), 5.02 (d, *J* = 4.4 Hz, 2H, CH_2N), 3.76 (s, 3H, NCH_3), 2.62 (s, 3H, SCH_3), 2.34 (s, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 197.9, 137.0, 128.6, 126.9, 122.2, 119.7, 118.7, 109.5, 109.0, 43.0, 32.8, 18.0.

Synthesis of 1e and 1h

General procedure for the synthesis of dithiocarbamates 1e, 1f, and 1h and isothiocyanate 8

Methyl L-tryptophanate hydrochloride (**7**) was synthesized in a quantitive yield according to the method reported in literatures.[32] **7** (1.78 g, 7 mmol) and anhydrous Na_2CO_3 (0.45 g, 4.2 mmol) were dissolved in a mixture of methanol (20 mL) and water (1.5 mL) and the mixture was cooled to 0 °C. TEA (1.42 g, 1.95 mL, 14 mmol) and CS_2 (1.07 g, 0.85 mL, 14 mmol) were added into the mixture for 30 minutes then MeI (1.99 g, 0.87 mL, 14 mmol, for **1e**), or BnCl (0.93 g, 0.85 mL, 7.35 mmol, for **1f**), or 1-bromopropane (1.72 g, 1.28 mL, 14 mmol, for **1h**) was added into the reaction system. The whole mixture was stirred for 20 min and then warmed up to room temperature until the reaction was finished monitored by TLC (ca. 2 h). After removal of solvent, water (60 mL) was added and the aqueous phase was extracted with EtOAc (3 × 70 mL). The organic layer was dried over anhydrous Na_2SO_4 and followed by removal of solvent. The pure dithiocarbamates **1e** (1.94 g), **1f** (0.94 g) and **1g** (1.27 g) were obtained after the purification of column chromatography with PE/EA = 20/1 – 10/1 – 4/1 as eluent. Isothiocyanate **8** was isolated (0.4 g, 22% yield) as a byproduct in the reaction system of **1f**.

Methyl ((methylthio)carbonothioyl)-*L*-tryptophanate (**1e**): Sticky colorless oil, 1.94 g, the two-step yield was 90% from methyl L-tryptophanate hydrochloride (**7**). IR ($CHCl_3$) (cm^{-1}): 3403, 2951, 1733, 1490, 1356, 1213, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 1H, NH), 7.51 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.41 (d, *J* = 7.6 Hz, 1H, NHCS), 7.34 (dd, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.19 (dt, *J* = 8.0, 1.2 Hz, 1H, ArH), 7.12 (dt, *J* = 8.0, 1.2 Hz, 1H, ArH), 6.95 (d, *J* = 2.4 Hz, 1H, ArH), 5.56 (ddd, *J* = 7.6, 4.8, 4.8 Hz, 1H, $CHCO_2Me$), 3.69 (s, 3H, CO_2Me), 3.60 (dd, *J* = 14.8, 4.8 Hz, 1H, CH_2CH), 3.40 (dd, *J* = 14.8, 4.8 Hz, 1H, CH_2CH), 2.57 (s, 3H, SCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.9, 171.3, 136.0, 127.5, 122.9, 122.3, 119.8, 118.6, 111.2, 109.5, 59.4, 52.6, 26.7, 18.1.

Methyl ((benzylthio)carbonothioyl)-*L*-tryptophanate (1f)

Sticky yellow oil, 0.94 g, the two-step yield was 35% from **7**. IR ($CHCl_3$) (cm^{-1}): 3411, 1736, 1494, 1341, 1212, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1H, NH), 7.48 (d, *J* = 8.0 Hz, 1H, ArH), 7.40 (d, *J* = 6.8 Hz, 1H, NHCS), 7.25 – 7.32 (m, 6H, ArH), 7.17 (dd, *J* = 7.2, 7.6 Hz, 1H, ArH), 7.07 (dd, *J* = 7.2, 7.6 Hz, 1H, ArH), 6.85 (d, *J* = 1.6 Hz, 1H, ArH), 5.54 ((ddd, *J* = 4.4, 5.6, 6.8 Hz, 1H, $CHCO_2Me$), 4.49 (d, *J* = 13.6 Hz, 1H, SCH_2), 4.43 (d, *J* = 13.6 Hz, 1H, SCH_2), 3.66 (s, 3H, CO_2Me), 3.59 (dd, *J* = 5.6, 14.8 Hz, 1H, CH_2CH), 3.37 (dd, *J* = 4.4, 14.8 Hz, 1H, CH_2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 197.4, 171.2, 136.1, 136.0, 129.0, 128.6, 127.5, 122.9, 122.3, 119.8, 118.6, 111.2, 109.3, 59.4, 52.6, 39.8, 26.6. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{20}H_{21}N_2O_2S_2^+$, 385.1039. Found: 385.1043.

Methyl ((propylthio)carbonothioyl)-*L*-tryptophanate (1g)

Sticky pale yellow oil, 1.27 g, the two-step yield was 54% from **7**. IR ($CHCl_3$) (cm^{-1}): 3349, 2972, 1735, 1488, 1457, 1091, 1049, 909. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1H, NH), 7.51 (d, *J* = 7.6 Hz, 1H, ArH), 7.38 – 7.34 (m, 2H, the signal of NHCS overlapped with ArH), 7.20 (ddd, *J* = 7.6, 6.8, 1.2 Hz, 1H, ArH), 7.12 (ddd, *J* = 8.0, 6,8, 1.2 Hz, 1H, ArH), 6.96 (d, *J* = 2.4 Hz, 1H, ArH), 5.56 (ddd, *J* = 7.6, 5.2, 4.4 Hz, 1H, $CHCO_2$), 3.70 (s, 3H, CO_2Me), 3.62 (dd, *J* = 14.8, 5.2 Hz, 1H, CH_2CH), 3.40 (dd, *J* = 14.8, 4.4 Hz, 1H, CH_2CH), 3.21 (dt, *J* = 13.2, 7.2 Hz, 1H, SCHH), 3.16 (dt, *J* = 13.2, 7.2 Hz, 1H, SCHH), 1.69 (sextet, *J* = 7.2 Hz, 2H, CH_2), 0.99 (s, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 198.4, 171.4, 136.0, 127.6, 122.9, 122.3, 119.8, 118.7, 111.2, 109.6, 59.2, 52.5, 37.2, 26.7, 22.3, 13.4. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{16}H_{21}N_2O_2S_2^+$, 337.1039. Found: 337.1040.

Methyl (*S*)-3-(*1H*-indol-3-yl)-2-isothiocyanatopropanoate (8)

Sticky yellow oil, 0.4 g, the two-step yield was 22% from **7**. IR ($CHCl_3$) (cm^{-1}): 3410, 2924, 2069, 1742, 1213, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1H, NH), 7.56 (d, *J* = 8.0 Hz, 1H, ArH), 7.36 (d, *J* = 8.4 Hz, 1H, ArH), 7.19 (dt, *J* = 0.8, 7.2 Hz, 1H, ArH), 7.17 – 7.13 (m, 2H, ArH), 4.57 (dd, *J* = 4.8, 8.0 Hz, 1H, $CHCO_2Me$), 3.44 (dd, *J* = 4.8, 14.4 Hz, 1H, CH_2), 3.34 (dd, J = 8.0, 14.8 Hz, 1H, CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.7, 126.8, 124.0, 122.3, 119.8, 111.4, 109.1, 60.2, 53.1, 30.0. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{13}H_{13}N_2O_2S^+$, 261.0692. Found: 261.0693.

Procedure for the synthesis of dithiocarbamates 1h[44]

Methyl (*S*)-3-(*1H*-indol-3-yl)-2-isothiocyanatopropanoate (**8**) (0.56 g, 2.15 mmol), thiophenol (355 mg, 0.33 mL, 3.23 mmol) and TEA (218 mg, 0.3 mL, 2.15 mmol) were added into 10 mL of dry toluene and the mixture was refluxed for 8 h. The whole system was cooled to room temperature. After evaporation of solvent, the residue was submitted to the column chromatography with PE/EA = 20/1 – 10/1 – 2/1 as eluent to afford the target product **1h**. Pale yellow solid, 493 mg, yield 62%, m.p. 124–126 °C (DCM/*n*-Hexane). IR ($CHCl_3$) (cm^{-1}): 3399, 3321, 1737, 1489, 1375, 1213, 745. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (s, 1H, NH), 7.49 (d, *J* = 8.0 Hz, 1H, ArH), 7.34 (m, 2H, ArH), 7.22 (m, 2H, ArH), 7.17 (m, 3H, ArH), 7.02 (ddd, *J* = 6.8 Hz, 1H, ArH), 6.68 (ddd, *J* = 2.4 Hz, 1H, ArH), 5.39 (ddd, *J* = 4.0, 5.6, 7.2 Hz, 1H, $CHCO_2$), 3.66 (s, 3H, CO_2Me), 3.60 (dd, *J* = 5.6, 4.8 Hz, 1H in CH_2CH), 3.27 (dd, *J* = 4.0, 14.8 Hz, 1H in CH_2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 195.0, 171.0, 135.9, 135.3, 130.9, 130.0, 127.6, 127.6, 122.4, 122.4, 120.0, 118.7, 111.1, 109.2, 58.4, 52.6, 26.1. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{19}H_{19}N_2O_2S_2^+$, 371.0882. Found: 371.0888.

General procedure of Cyclobrassinin (2a) and its analogues (2)

Under the nitrogen protection, dithiocarbamate **1** (0.5 mmol) and benzoyl peroxide [(182 mg, 0.75 mmol for **1a**, **1b** and **1g**), (121 mg, 0.5 mmol for **1c**-**1f** and **1g**)] was dissolved in 1,2-dichloroethane (2.5 mL). The reaction mixture vessel was put into a pre-heated oil bath

View Article Online
DOI: 10.1039/C8NJ02037J

to reflux for 2 h. Then the system was allowed to cool to room temperature and was washed with satuarated $NaHCO_3$ aqueous solution (8 mL) to remove benzoic acid. The aqueous phase was extracted with 1,2-dichloroethane (2 × 9 mL) and then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel with a mixture of PE and EtOAc (50 : 1 – 40 : 1,, *v*/*v*, for **2a**-**2d** , 30 : 1 – 20 : 1, *v*/*v*, for **2e**-**2h**) as the eluent to afford the desired cyclization product **2**.

2-(Methylthio)-4,9-dihydro-[1,3]thiazino[6,5-*b*]indole (cyclobrassinin; 2a)

Colorless solid, 37 mg, yield 32%, m.p. 139 – 140 °C(PE/EtOAc), lit. m. p. 136–137 °C.[10] IR ($CHCl_3$) (cm^{-1}): 3390, 3373, 2851, 1598, 1448, 1426. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.44 (s, 1H, NH), 7.48 (d, *J* = 8.0 Hz, 1H, H-5), 7.33 (d, *J* = 8.0 Hz, 1H, H-8), 7.09 (dt, *J* = 1.2, 8.0 Hz, 1H, H-7), 7.03 (dt, *J* = 1.2, 8.0 Hz, 1H, H-6), 5.06 (s, 2H, CH_2), 2.53 (s, 3H, SCH_3) ppm. ^{13}C NMR (100.6 MHz, DMSO-*d*6): δ = 150.7(C-2), 136.5 (C-8a), 124.5 (C-4b), 121.4 (C-9a), 121.3 (C-7), 119.3 (C-6), 117.0 (C-5), 111.0 (C-8), 101.6 (C-4a), 48.0 (C-4), 14.6 (CH_3).

9-Methyl-2-(methylthio)-4,9-dihydro-[1,3]thiazino[6,5-*b*]indole (2c)

Yellow solid, 66 mg, yield 53%, m.p. 105–106 °C ($CHCl_3$), lit. m. p. 97–99 °C.[30] IR ($CHCl_3$) (cm^{-1}): 3342, 2971, 2925, 1615, 1465, 1091, 1050. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.6 Hz, 1H, ArH), 7.28 (d, *J* = 8.4 Hz, 1H, ArH), 7.19 (ddd, *J* = 0.8, 7.2, 8.0 Hz, 1H, ArH), 7.12 (ddd, *J* = 0.8, 7.2, 7.6 Hz, 1H, ArH), 5.08 (s, 2H, CH_2N), 3.63 (s, 2H, CH_3N), 2.55 (s, 3H, SCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.8, 125.2, 124.9, 121.4, 119.7, 117.2, 108.7, 102.6, 49.2, 30.0, 15.4.

9-Benzyl-2-(methylthio)-4,9-dihydro-[1,3]thiazino[6,5-*b*]indole (2d)

Yellow solid, 100 mg, yield 62%, m.p. 118–120 °C ($CHCl_3$). IR ($CHCl_3$) (cm^{-1}): 3054, 2924, 1615, 1495, 1453, 1337, 905, 739. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 – 7.08 (m, 9H, ArH), 5.21 (s, 2H, $ArCH_2$), 5.11 (s, 2H, CH_2N), 2.53 (s, 3H, SCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.1, 137.7, 136.8, 128.8, 127.7, 126.7, 125.2, 125.0, 121.6, 119.9, 117.2, 109.3, 103.1, 49.2, 47.4, 15.3. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{18}H_{17}N_2S_2^+$, 325.0828. Found: 325.0833.

Methyl (*S*)-2-(methylthio)-5,10-dihydro-4*H*-[1,3]thiazepino[7,6-*b*]indole-4-carboxylate (2e)

Pale yellow solid, 50 mg, yield 33%, m.p. 159–161°C ($CHCl_3$). $[\alpha]^{20}_D$ = +45.5 (c = 10 mg/mL, $CHCl_3$). IR ($CHCl_3$) (cm^{-1}): 3366, 2923, 2852, 1737, 1586, 1449, 1274. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H, NH), 7.40 (dd, *J* = 1.2, 7.6 Hz, 1H, ArH), 7.23 (dt, *J* = 1.2, 7.2 Hz, 1H, ArH), 7.16 (ddd, *J* = 1.2, 7.2, 7.6 Hz, 1H, ArH), 7.10 (ddd, *J* = 1.2, 7.2, 7.6 Hz, 1H, ArH), 5.12 (dd, *J* = 2.4, 12.0 Hz, 1H, $CHCO_2Me$), 3.86 (s, 3H, CO_2Me), 3.54 (dd, *J* = 2.4, 16.4 Hz, 1H in CH_2CH), 3.19 (dd, *J* = 12.0, 16.4 Hz, 1H in CH_2CH), 2.44 (s, 3H, SCH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 158.7, 135.0, 128.6, 122.8, 120.0, 119.3, 117.7, 111.0, 110.4, 64.5, 52.5, 27.0, 16.0 ppm. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{14}H_{15}N_2O_2S_2^+$, 307.0569. Found: 307.0565.

Methyl (*S*)-2-(benzylthio)-5,10-dihydro-4*H*-[1,3]thiazepino[7,6-*b*]indole-4-carboxylate (2f)

Yellow oil, 55 mg, yield 29%, $[\alpha]^{20}_D$ = +3.2 (c = 4 mg/mL, $CHCl_3$). IR ($CHCl_3$) (cm^{-1}): 3383, 3060, 2924, 1733, 1584, 1451, 1276. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1H, NH), 7.42 (d, *J* = 7.6 Hz, 1H, ArH), 7.35 – 7.23 (m, 6H, ArH), 7.17(dt, *J* = 0.8, 7.2 Hz, 1H, ArH), 7.11 (dt, *J* = 0.8, 7.2 Hz, 1H, ArH), 5.12 (dd, *J* = 2.4, 12.0 Hz, 1H, $CHCO_2Me$), 4.39 (d, *J* = 13.6 Hz, 1H, SCH_2), 4.14 (d, *J* = 13.6 Hz, 1H, SCH_2), 3.88 (s, 3H, CO_2Me), 3.56 (dd, *J* = 2.4, 16.4 Hz, 1H, CH_2CH), 3.19 (dd, *J* = 12.0, 16.4 Hz, 1H, CH_2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.6, 157.3, 136.7, 135.0, 129.2, 128.6, 128.5, 127.3, 122.9, 120.2, 119.2, 117.8, 111.2, 110.4, 64.6, 52.4, 37.3, 27.0. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{20}H_{19}N_2O_2S_2^+$, 383.0882. Found: 383.0873.

Methyl (*S*)-2-(propylthio)-5,10-dihydro-4*H*-[1,3]thiazepino[7,6-*b*]indole-4-carboxylate (2g)

Yellow oil, 50 mg, yield 30%, $[\alpha]^{20}_D$ = +0.70 (c = 7 mg/mL, $CHCl_3$). IR ($CHCl_3$) (cm^{-1}): 3361, 2961, 1736, 1586, 1450, 1435, 1275, 741. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1H, NH), 7.41 (d, *J* = 8.0 Hz, 1H, ArH), 7.24 (d, *J* = 8.4 Hz, 1H, ArH), 7.17(t, *J* = 7.2 Hz, 1H, ArH), 7.10 (t, *J* = 7.2 Hz, 1H, ArH), 5.10 (dd, *J* = 2.4, 12.0 Hz, 1H, $CHCO_2$), 3.85 (s, 3H, CO_2Me), 3.55 (dd, *J* = 2.4, 16.4 Hz, 1H in CH_2CH), 3.18 (dd, *J* = 12.0, 16.4 Hz, 1H in CH_2CH), 3.12 (dt, *J* = 13.2, 7.2, 1H in SCH_2), 2.89 (dt, *J* = 13.2, 7.2, 1H in SCH_2), 1.68 (sextet, *J* = 7.2 Hz, 2H, CH_2), 0.97 (s, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.7, 158.0, 135.0, 128.6, 122.8, 120.1, 119.6, 117.7, 111.1, 110.4, 64.5, 52.4, 34.9, 26.9, 21.9, 13.4. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{16}H_{19}N_2O_2S_2^+$, 335.0882. Found: 335.0885.

Methyl (*S*)-2-(phenylthio)-5,10-dihydro-*4H*-[1,3]thiazepino[7,6-*b*]indole-4-carboxylate (2h)

Yellow oil, 15 mg, yield 15%. IR ($CHCl_3$) (cm^{-1}): 3359, 2917, 1734, 1593, 1472, 1450, 1271, 742. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H, NH), 7.54 (m, 2H, ArH), 7.42 (d, *J* = 8.0 Hz, 1H, ArH), 7.35 (m, 3H, ArH), 7.24 (d, *J* = 7.2 Hz, 1H, ArH), 7.18(dd, *J* = 6.8, 8.0 Hz, 1H, ArH), 7.11 (dt, *J* = 7.6, 7.2 Hz, 1H, ArH), 5.12 (dd, *J* = 2.4, 12.0 Hz, 1H, $CHCO_2Me$), 4.39 (d, *J* = 13.6 Hz, 1H in SCH_2), 4.14 (d, *J* = 13.6 Hz, 1H in SCH_2), 3.88 (s, 3H, CO_2Me), 3.56 (dd, *J* = 2.4, 16.4 Hz, 1H in CH_2CH), 3.19 (dd, *J* = 12.0, 16.4 Hz, 1H in CH_2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.1, 158.2, 136.9, 135.0, 133.5, 129.1, 128.9, 128.6, 123.0, 120.2, 119.3, 117.9, 111.4, 110.4, 64.9, 52.4, 26.6. HRMS (ESI), *m/z*, calcd for $[M+H]^+$: $C_{19}H_{17}N_2O_2S_2^+$, 369.0726. Found: 369.0728.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Nos. 21572017, 21772010, and 21702014). Mr. Xiang Li and Mr. Jun Dong are greatly appreciated for their generous helps for the replication experiments after the graduation of Xin Zhong.

View Article Online
DOI: 10.1039/C8NJ02037J

Notes and references

1 R. G. Mehta, J. Liu, A. Constantinou, C. F. Thomas, M. Hawthorne, M. You, C. Gerhauser, J. M. Pezzuto, R. C. Moon and R. M. Moriarty, *Carcinogenesis,* 1995*,* **16***,* 399.

2 I. Ahuja, J. Rohloff and A. M. Bones, *Agron. Sustain. Dev.* 2010, **30**, 311.

3 P. Bednarek and A. Osbourn, *Science* 2009, **324(5928)**, 746.

4 J. V. Higdon, B. Delage, D. E. Williams and R. H. Dashwood, *Pharmacol Res*. **2007**, 55, 224.

5 M. Mazzola, S. S. Hewavitharana and S. L. Strauss, *Phytopathology* 2015, **105**, 460.

6 Z. R. Hansen, A. P. Keinath, *Appl. Soil. Ecol.* 2013, **63**, 67.

7 A. P. Klein, E. S. Sattely, *Proc. Natl. Acad. Sci. U. S. A.* 2017**, 114**, 1910.

8 M. S. C. Pedras, E. E. Yaya, E. Glawischnig, *Nat. Prod. Rep.* 2011**, 28**, 1381.

9 M. S. C. Pedras, Q. H. To, *Chem. Commun.* 2016, **52**, 5880.

10 M. Takasugi, K. Monde, N. Katsui, A. Shirata, *Bull. Chem. Soc. Jpn*. 1988, **61**, 285.

11 P. Kutschy, M. Suchy, K. Monde, N. Harada, R. Maruskova, Z. Curillova, M. Dzurilla, M. Miklosova, R. Mezencev, J. Mojzis, *Tetrahedron Lett.* 2002, **43**, 9489.

12 P. Csomós, L. Fodor, P. Sohár, G. Bernáth, *Tetrahedron*, 2005, **61**, 9257.

13 F. De Vleeschouwer, V. Van Speybroeck, M. Waroquier, P. Geerlings, F. De Proft, *Org. Lett.* 2007**, 9**, 2721.

14 I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* 2011**, 111**, 1596.

15 M. Arisawa, *Tetrahedron Lett.* 2014**, 55**, 3391.

16 S. K. R. Parumala, R. K. Peddinti, *Green Chem*. 2015, **17**, 4068.

17 Z. Huang, D. Zhang, X. Qi, Z. Yan, M. Wang, H. Yan, A. Lei, *Org. Lett.* 2016**, 18**, 2351.

18 Y. Liu, Y. Zhang, C. Hu, J. P. Wan, C. Wen, *RSC Adv.* 2014**, 4**, 35528.

19 P. Wang, S. Tang, P. Huang, A. Lei, *Angew. Chem. Int. Ed.* 2017**, 56***,* 3009.

20 T. Gensch, F. J. R. Klauck, F. Glorius, *Angew. Chem. Int. Ed.* 2016**, 55**, 11287.

21 C. Chatgilialoglu, M. P. Bertrand, C. Ferreri, In S-Centered Radicals. Ed. Z. B. Alfassi, John Wiley & Sons: Chichester, **1999**.

22 M. P. Bertrand, C. Ferreri, Sulfer-Centered Radicals. Ed. P. Renaud, M. P. Sibi, Wiley-VCH, Weinheim, **2001**.

23 F. Dénès, M. Pichowicz, G. Povie and P. Renaud, *Chem. Rev*., 2014, **114**, 2587-2693..

24 L. Markey, S. Giordani, E. M. Scanlan, *J. Org. Chem*. 2013, **78**, 4270.

25 N. B. Cramer, S. K. Reddy, K. O'Brien, C. N. Bowman, *Macromolecules* 2003, **36**, 7964.

26 S. Suzuki, E. Perrier, T. Urano, S. Takahara, T. Yamaoka, *Polymer* 2005, **46**, 2238.

27 E. C. Kooyman, *Pure. Appl. Chem.* 1967, **15**, 81.

28 S. Kakaei, J. X. Xu, *Org. Biomol. Chem*. 2013, **11**, 5481.

29 N. Chen, X. Zhong, P. F. Li, J. X. Xu, *Eur. J. Org. Chem*. 2015, 802.

30 P. Kutschy, M. Dzurilla, M. Takasugi, M. Török, I. Achbergerová, R. Homzová, M. Ráczová, *Tetrahedron* 1998, **54**, 3549.

31 J. Soubhye, M. Prévost, P. Van Antwerpen, K. Zouaoui Boudjeltia, A. Rousseau, P. G. Furtmüller, C. Obinger, M. Vanhaeverbeek, J. Ducobu, J. Nève, M. Gelbcke, F. O. Dufrasne, *J. Med. Chem.* 2010**, 53**, 8747.

32 Y. Zhang, P. Yang, C. J. Chou, C. Liu, X. Wang, W. Xu, *ACS Med. Chem. Lett.* 2013**, 4**, 235.

33 In xanthate and dithiocarbamate chemistry, dilauroyl peroxides are frequently used as radical initiator, but BPO was seldom. M. El Qacemi, L. Petit, B. Quiclet-Sire, S. Z. Zard, *Org. Biomol. Chem.* 2012**, 10**, 5707.

34 B. Quiclet-Sire, S. Z. Zard, *Chem. - Eur. J.* 2006**, 12**, 6002.

35 S. M. Gao, Y. Zhang, J. Dong, N. Chen, J. X. Xu, *Org. Biomol. Chem.* 2016**, 14**, 1002.

36 S. M. Allin, W. R. S. Barton, W. Russell Bowman, E. Bridge, M. R. J. Elsegood, T. McInally and V. McKee, *Tetrahedron* 2008, **64**, 7745.

37 A. Servais, M. Azzouz, D. Lopes, C. Courillon and M. Malacria, *Angew. Chem. Int. Ed.* 2007, **46**, 576.

38 S.-Y. Sit, K. Xie, S. Jacutin-Porte, M. T. Taber, A. G. Gulwadi, C. D. Korpinen, K. D. Burris, T. F. Molski, E. Ryan, C. Xu, H. Wong, J. Zhu, S. Krishnananthan, Q. Gao, T. Verdoorn and G. Johnson, *J. Med. Chem.* 2002, **45**, 3660.

39 B. Quiclet-Sire, N. D. M. Tran and S. Z. Zard, *Org. Lett.* 2012, **14**, 5514-5517.

40 H. Zhang, E. B. Hay, S. J. Geib and D. P. Curran, *Beilstein J. Org. Chem.*, 2015, **11**, 1649.

41 H. Zhang, E. B. Hay, S.J. Geib and D. P. Curran, *J. Am. Chem. Soc.* 2013, **135**, 16610.

42 For an example on acyl radical cyclization, 5-*exo*-trig is 10 times faster than 6-*endo*-trig. C. Chatgilialoglu, C. Ferreri, M. Lucarini, A. Venturini and A. A. Zavitsas, *Chem. Eur. J.* 1997**, 3**, 376.

43 J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.* 1977**, 42**, 3846.

44 Y. Hagooly, J. Hagooly, A. Hagooly and S. Rozen, *J. Org. Chem*. 2009, **74**, 8578.